

Glycopyrronium bromide (SPOT-List)

Glycopyrronium is one of the items on the PrescQIPP SPOT-List (Specials Prescribing Optimisation Tool). During the period of July to September 2016, in England and Wales, over £2 million was spent on glycopyrronium products (excluding inhaled glycopyrronium). Glycopyrronium is used for a range of indications. These include hypersalivation, hyperhidrosis, treatment of peptic ulcers, chronic obstructive pulmonary disease (COPD), plus other licensed indications listed below. The main focus of this bulletin is the use of unlicensed/off label glycopyrronium bromide for hypersalivation.

Recommendations

- Consider whether there is a continued need for prescribing unlicensed or off label glycopyrronium in any indication.
- Consider the need for glycopyrronium bromide for drooling, as there is limited evidence for its use and it is not licensed for this indication.
- If a patient requires glycopyrronium bromide for off label or unlicensed indications, consider whether it is appropriate for prescribing locally. Management and review of patients should remain with the specialist.
- Licensed 1mg and 2mg tablets and a licenced 1mg/5ml oral solution are available for the treatment of peptic ulcers in adults. Consider the off label use of these tablets or oral solution instead of unlicensed specials in other indications if glycopyrronium treatment is necessary.

Hypersalivation is also known as drooling or sialorrhoea. First line management of drooling should be directed at the cause, which may be multi-factorial and patient specific. There are various drug treatments, which have been used in the management of hypersalivation. None of these drugs are licensed in the UK for the treatment of hypersalivation. Examples include:¹

- Antimuscarinic drugs (amitriptyline, atropine, benztropine, trihexyphenidyl hydrochloride (benzhexol hydrochloride, glycopyrronium bromide (glycopyrrolate)): oral, nebulised and subcutaneous.
- Hyoscine hydrobromide (scopolamine hydrobromide): oral, topical, subcutaneous and nebulised.
- Beta-blockers.
- Botulinum toxin.

Glycopyrronium bromide will be the focus of this bulletin. However, summarised evidence will be included for some of the other treatments.

Glycopyrronium bromide

Glycopyrronium is an antimuscarinic compound, which is structurally related to atropine. It is a long acting preparation that does not cross the blood-brain barrier, therefore central side effects are greatly reduced. This is an advantage over benztropine, hyoscine and trihexyphenidyl hydrochloride, which are also used to treat hypersalivation.² Glycopyrronium has an extremely variable and incomplete gastrointestinal absorption followed by a late clinical response. However there is some evidence that even low plasma concentrations cause a significant reduction in saliva flow.²

Various licenced glycopyrronium bromide preparations are available which are licenced for one or more of the following indications:

- To protect against the peripheral muscarinic actions of anticholinesterases such as neostigmine and pyridostigmine, used to reverse residual neuromuscular blockade produced by non-depolarising muscle relaxants.³
- As a pre-operative antimuscarinic agent to reduce salivary tracheobronchial and pharyngeal secretions and to reduce the acidity of the gastric contents.³
- As a pre-operative or intra-operative antimuscarinic, to attenuate or prevent intra-operative bradycardia associated with the use of suxamethonium or due to cardiac vagal reflexes.³
- Maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).⁴
- For use in adults as add-on therapy in the treatment of peptic ulcers.⁵

Glycopyrronium bromide can also be used for hyperhidrosis (excessive sweating). There is no randomised controlled trial evidence of the use of oral glycopyrronium bromide for hyperhidrosis. Glycopyrronium is only licensed for treating excessive sweating if used in an electrical treatment called 'iontophoresis' for the palms of the hands and soles of the feet. When glycopyrronium is taken by the mouth (orally) as tablets or as a liquid for treating excessive sweating, this use is unlicensed in the UK. There is some weak evidence from case series that oral glycopyrronium bromide tablets reduce sweating in people with hyperhidrosis.⁶

Glycopyrronium bromide does not have a marketing authorisation in the UK for treating hypersalivation in children, young people or adults. Oral preparations of glycopyrronium bromide tablets (1mg/2mg) and 1mg/5ml oral solution are available in the UK. These are licensed for the treatment of peptic (stomach) ulcers in adults. Use of glycopyrronium to treat peptic ulcers is well established in medical practice and documented in the scientific literature.¹ In addition, glycopyrrolate (glycopyrronium bromide) 1mg/5 ml oral solution (Cuvposa) was licensed in the USA in 2010. This was for treating chronic severe drooling in children and young people aged three to 16 years with neurological conditions associated with problem drooling, for example, cerebral palsy.⁷

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using glycopyrronium bromide outside its authorised indications.⁷ Prescribing glycopyrronium bromide tablets for hypersalivation is considered an unlicensed use of the medication.

Evidence available

The National Institute of Health and Care Excellence (NICE) have produced evidence summaries of off label and unlicensed uses of oral glycopyrronium. One summary covers the treatment of hypersalivation in different age groups/conditions. Some of doses ranged from 0.02mg/kg to 0.1mg/kg, however there were several variations of dosing used in different trials. The main points are summarised below:⁷

Use in children and young people⁷

Two small, double-blind, placebo-controlled, randomised controlled trials (RCTs) were identified. These evaluated the efficacy and safety of oral glycopyrronium bromide for treating drooling in children and young people with a neurological condition. Parent (or carer) reported drooling was significantly improved.

Oral glycopyrronium bromide was frequently associated with adverse effects in the two trials in children and young people with a neurological condition. More people stopped glycopyrronium bromide treatment because of adverse effects, compared with those taking placebo. More people reported serious adverse effects with glycopyrronium bromide compared with placebo. The statistical significance was not reported.

The identified placebo-controlled RCTs provide moderate evidence that oral glycopyrronium bromide reduces drooling, but increases antimuscarinic adverse effects, compared with placebo. However, all the RCTs were small, with fewer than 40 participants in each trial, and were also short term. They do not provide evidence of the long-term use of oral glycopyrronium bromide for treating hypersalivation in adults, children and young people.

In the two trials in children and young people, more adverse effects were reported in the groups receiving glycopyrronium bromide than those receiving placebo. The statistical significance of differences between the groups was not reported in either study.

The most commonly reported adverse effects in these trials were:

- Behavioural changes (e.g. drowsiness, restlessness, hyperactivity and irritability).
- Excessively dry mouth
- Constipation
- Urinary retention
- Vomiting
- Nasal congestion
- Flushing.

Use in adults⁷

One double-blind, placebo-controlled RCT was identified which examined the efficacy and safety of oral glycopyrronium bromide for treating hypersalivation in adults with Parkinson's disease.

An additional RCT was identified comparing oral glycopyrronium bromide with the centrally acting antimuscarinic biperiden for treating clozapine-induced hypersalivation in adults with schizophrenia (unlicensed use). All of the identified trials were small, with fewer than 40 participants in each trial, and were short term (eight weeks or less).

The RCT in adults with Parkinson's disease showed a significant improvement in drooling score. This was with one week of glycopyrronium bromide 1mg three times daily compared with placebo.

The RCT in adults with schizophrenia and clozapine-induced hypersalivation, showed that drooling improved. This was with either oral glycopyrronium bromide 1mg twice daily or oral biperiden 2mg twice daily (a centrally acting antimuscarinic agent) for four weeks. Drooling significantly improved from baseline with both medicines, but glycopyrronium bromide was superior. Participants taking biperiden had a significant reduction in Mini Mental State Examination (MMSE) scores; there were no significant differences from baseline in MMSE scores with glycopyrronium bromide.

Glycopyrronium tablets have a UK licence and more recently glycopyrronium bromide 1mg/5ml oral solution has been granted a UK licence for treatment of peptic ulcer. However hypersalivation is an unlicensed use of these products. Using a UK licensed product in this manner is category B under the MHRA hierarchy of risk. This is a lower net risk and preferred over an unlicensed liquid special https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/373505/The_supply_of_unlicensed_medicinal_products__specials_.pdf

The glycopyrronium injection has previously been used orally and administered via an enteral feeding tube.⁸ The Drug Tariff varies in price for various strengths of the unlicensed glycopyrronium bromide oral solutions and suspensions.⁹ There is no conclusive evidence available for the recommended strength of glycopyrronium bromide that should be used for treatment.

Consider commissioning arrangements locally for the recommending specialist to continue prescribing the medication where possible. If a child requires the medication, consider licensed liquid being used for an unlicensed indication or if they are able to swallow tablets consider using the tablet formulation.

NICE has issued a clinical guideline on the diagnosis and management on Parkinson's disease in the over 20s, which states that people with Parkinson's disease should be treated appropriately for drooling

(sialorrhoea).¹⁰ The full clinical guideline states that management may include drug treatment, such as sublingual 1% atropine ophthalmic solution twice daily, or injection of salivary glands with botulinum toxin A. (Neither of these are licensed in the UK for treating hypersalivation). There is no reference to the use of glycopyrronium bromide in the clinical guideline.¹⁰

The evidence base for using glycopyrronium bromide is very weak, and its use for hypersalivation should be reviewed on a regular basis. If there has been no improvement, it should be discontinued.

Other treatments available for hypersalivation

There are alternative drugs to glycopyrronium bromide that have been used for treatment of hypersalivation, however none of them are licensed for the treatment of hypersalivation. The alternatives include hyoscine hydrobromide, amitriptyline, atropine and botulinum.

Hyoscine hydrobromide¹¹

- None of the hyoscine hydrobromide preparations currently available in the UK are licensed to treat hypersalivation.
- Although there are no published studies, oral or subcutaneous hyoscine hydrobromide has been used anecdotally for the management of hypersalivation.
- Transdermal hyoscine patches offer several advantages over other treatments including ease of administration, maintenance of steady state concentrations and a low incidence of systemic side effects compared with other anticholinergics
- Hyoscine patches may be particularly useful for patients with intractable swallowing difficulties (e.g. head and neck cancers) who may have problems with drooling or choking owing to the normal production of saliva.
- Data on long-term efficacy and safety of hyoscine by any route are exceedingly sparse.

Amitriptyline¹²

- There are no published reports of the use of amitriptyline in the management of hypersalivation.
- It has been used anecdotally, but its sedative properties may limit its use to patients experiencing hypersalivation at night.

Atropine¹²

- In the NICE full Clinical Guideline on the management of Parkinson's disease, sublingual 1% atropine ophthalmic solution twice daily is one option suggested for the treatment of hypersalivation, as mentioned above.
- A small randomised double-blind, cross-over placebo-controlled trial which evaluated the effectiveness of sublingual atropine sulfate drops for the management of hypersalivation failed to demonstrate any significant benefits.
- One small non-comparative study has investigated the use of sublingual atropine for the treatment of hypersalivation in seven patients with parkinsonism. One patient withdrew because of delirium (concurrent with a urinary infection) and two patients experienced worsening of hallucinations (pre-existing active hallucinosis was concealed by both patients). No other side effects were reported. Participants demonstrated statistically significant reductions in saliva production both subjectively and objectively.
- Other studies were also observed, with similar outcomes. However, further studies are required to determine if, and under what circumstances, sublingual atropine is effective for the management of hypersalivation.

Botulinum toxin

- In the NICE full Clinical Guideline on the management of Parkinson's disease, injection of salivary glands with botulinum toxin A is one option suggested for the treatment of hypersalivation.¹³
- UKMI have produced a review of treatments used in hypersalivation. Other treatments considered in this review are benztropine, trihexphenidyl hydrochloride (benzhexol hydrochloride), beta blockers, ipratropium bromide, and modafinil. They state that evidence for these treatments is limited. They summarised the following:¹²
 - » A Cochrane review examining interventions for drooling in children with cerebral palsy was unable to reach a conclusion on the effectiveness or safety of either botulinum toxin A, benztropine or glycopyrronium. Insufficient evidence was found to inform clinical practice for the management of drooling in this patient group.
 - » The dose of oral benztropine, which can be given as a single daily dose, should be titrated individually for each patient, starting with a low dose and increasing, as indicated, by small weekly increments until therapeutic benefit is achieved or side effects occur. Benztropine often produces sedation, or less commonly, dysphoria and restlessness. Benztropine tablets are no longer available in the UK but can be imported from abroad. Trihexyphenidyl (benzhexol) is an alternative.
 - » The authors of one small non-comparative study suggest that the advantages of sublingually administered atropine include its availability as eye drops, low cost and reversibility. However, some patients may have difficulty manipulating the dropper to ensure proper dosing and there is the potential for accidental overdose with drops. The exact dose of sublingual atropine has not been established. Also atropine should not be used in patients with cognitive impairment, dementia and hallucinations. One small randomised placebo-controlled trial which evaluated the effectiveness of sublingual atropine sulfate drops for the management of hypersalivation, failed to demonstrate any significant benefits.
 - » There are two case reports of modafinil producing a dramatic improvement in drooling in two children with spastic cerebral palsy.
 - » Beta-blockers may be a useful "add-on" option with antimuscarinic drugs in some patients with amyotrophic lateral sclerosis/motor neuron disease.
 - » Botulinum toxin injections can be effective in certain circumstances, but require specialist expertise for administration.

Costs and savings

Licensed products

| Product | Quantity | Cost |
|--|----------|---------|
| Glycopyrronium bromide 1mg tablets ⁹ | 30 | £177.00 |
| Glycopyrronium bromide 2mg tablets ⁹ | 30 | £204.00 |
| Glycopyrronium bromide bromide 1mg/5ml oral solution ¹⁴ | 150ml | £91.00 |

Drug Tariff specials⁹

| Preparation | Minimum volume | Price for minimum volume | Price for each extra ml/g above minimum volume (pence) |
|---|----------------|--------------------------|--|
| Glycopyrronium bromide 1mg/5ml oral solution/suspension | 100ml | £101.25 | 3 |
| Glycopyrronium bromide 2.5mg/5ml oral solution | 100ml | £301.14 | 13 |
| Glycopyrronium bromide 2.5mg/5ml oral suspension | 200ml | £149.15 | 13 |
| Glycopyrronium bromide 200mcg/5ml oral solution | 100ml | £129.77 | 7 |
| Glycopyrronium bromide 200mcg/5ml oral suspension | 100ml | £76.81 | 4 |
| Glycopyrronium bromide 2mg/5ml oral solution | 100ml | £179.85 | 2 |
| Glycopyrronium bromide 2mg/5ml oral suspension | 100ml | £112.42 | 2 |
| Glycopyrronium bromide 5mg/5ml oral solution | 100ml | £138.31 | 3 |
| Glycopyrronium bromide 5mg/5ml oral suspension | 50ml | £60.24 | 46 |
| Glycopyrronium bromide 500mcg/5ml oral solution | 100ml | £159.27 | 9 |
| Glycopyrronium bromide 500mcg/5ml oral suspension | 300ml | £148.71 | 7 |

The cost of prescribing will depend on the amount prescribed. Using glycopyrronium 1mg/5ml oral solution/suspension as an example, the first 100ml will cost £101.25 then 3p per ml thereafter.

| Prescription | 150ml | 200ml |
|------------------|-----------------|------------------|
| First 100ml cost | £101.25 | £101.25 |
| Additional ml | 50 x 3p = £1.50 | 100 x 3p = £3.00 |
| TOTAL | £102.75 | £104.25 |

If the patient was given two scripts for 100ml then the cost would be 2 x £101.25 which is £202.50

In England and Wales, annual spend on glycopyrronium products (excluding inhaled treatments for COPD is over £17.1 million (ePACT July to September 2016).

There is limited evidence for the use of glycopyrronium bromide for hypersalivation, and it is not licensed for this indication. For this reason consider if there is a continued need for prescribing unlicensed or off label glycopyrronium .

If the patient does require glycopyrronium bromide for an off label or unlicensed indication, consider whether it is appropriate locally for GP prescribing or if prescribing responsibility should be retained by the specialist. If it is to be prescribed by GPs locally, it is important to consider licensing and cost. Consider undertaking a risk assessment and working with local hospital trusts, and agree a local decision for its use. This should include dose ranges to be used locally and also highlight the unlicensed nature of the treatment.

A 40% reduction in prescribing of glycopyrronium products/specials could lead to a saving of over £6.8 million across England and Wales (ePACT July to September 2016). This equates to £11,241 per 100,000 patients.

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Additional PrescQIPP resources



Briefing



Data pack

Available here: <https://www.prescqipp.info/resources/category/341-glycopyrronium-spot-list>

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